ORIGINAL ARTICLE

Mortality from non-malignant respiratory diseases among people with silicosis in Hong Kong: exposure–response analyses for exposure to silica dust

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Objectives: To examine the exposure–response relationships between various indices of exposure to silica dust and the mortality from non-malignant respiratory diseases (NMRDs) or chronic obstructive pulmonary diseases (COPDs) among a cohort of workers with silicosis in Hong Kong.

Methods: The concentrations of respirable silica dust were assigned to each industry and job task according to historical industrial hygiene measurements documented previously in Hong Kong. Exposure indices included cumulative dust exposure (CDE) and mean dust concentration (MDC). Penalised smoothing spline models were used as a preliminary step to detect outliers and guide further analyses. Multiple Cox's proportional hazard models were used to estimate the dust effects on the risk of mortality from NMRDs or COPDs after truncating the highest exposures.

Results: 371 of the 853 (43.49%) deaths occurring among 2789 workers with silicosis during 1981–99 were from NMRDs, and 101 (27.22%) NMRDs were COPDs. Multiple Cox's proportional hazard models showed that CDE ($p = 0.009$) and MDC ($p < 0.001$) were significantly associated only with NMRD mortality. Subgroup analysis showed that deaths from NMRDs ($p < 0.01$) and COPDs ($p < 0.05$) were significantly associated with both CDE and MDC among underground caisson workers and among those ever employed in other occupations with high exposure to silica dust. No exposure–response relationship was observed for surface construction workers with low exposures. A clear upward trend for both NMRDs and COPDs mortality was found with increasing severity of radiological silicosis.

Conclusion: This study documented an exposure–response relationship between exposure to silica dust and the risk of death from NMRDs or COPDs among workers with silicosis, except for surface construction workers with low exposures. The risk of mortality from NMRDs increased significantly with the progression of International Labor Organization categories, independent of dust effects.

Excessive mortality from non-malignant respiratory diseases (NMRDs) including chronic obstructive pulmonary disease (COPD) has been reported among cohorts exposed to silica dust or among cohorts with disease silicosis.[1–7] However, inconsistent or even conflicting evidence existed on the exposure–response relationship between exposure to silica dust and death from NMRDs or COPD.[1 3–9] Besides the potential differences in methods or toxicity of quartz polymorphs and exposure levels, discrepancies between studies might reflect the differences in biological effectiveness of various exposure indices.[3 10] The potential limitations of cumulative dust exposure (CDE) had been emphasised by Smith,[11] who said that CDE might be a poor dose index in examining the association with lung diseases by using a pharmacokinetic model. Hughes *et al*[12] found a substantially steeper relationship with silicosis among diatomaceous earth workers exposed at the highest concentrations of crystalline silica. More recently, Buchanan *et al*[13] provided supportive evidence on this issue and suggested that quantifying the risks of silicosis should take into account the variations in quartz exposure intensity, particularly for concentrations >1 or 2 mg/m^3, even if exposures were for relatively short periods. Studies comparing the possible effect of cumulative exposure to silica dust and mean dust concentration (MDC) on the risk of NMRD or COPD remain sparse and in demand. We report here the exposure–response analyses between various indices of exposure to silica dust and mortality from NMRDs or COPD among a cohort of 2789 workers with silicosis in Hong Kong, taking into consideration the effect of cigarette smoking.

METHODS

Details of cohort enumeration and follow-up of this study have been described elsewhere.[14] Briefly, the cohort comprised 2789 newly diagnosed male patients with silicosis seen at the Pneumoconiosis Clinic, Tuberculosis and Chest Service, Department of Health (Hong Kong SAR, China) from 1 January 1981 to 31 December 1998. All patients diagnosed with silicosis were entitled to compensation even if they were asymptomatic and with no loss of lung function. Each worker's demographic information, smoking habits, lifetime occupational history and medical history were obtained from medical records kept by the Pneumoconiosis Clinic. The presence of silicosis was defined as profusion category 1/0 or higher following the recommendation of the International Labor Organization (ILO).[15] Any discrepancy with regard to the classification of small or large opacities, if present, was resolved by consensus between the two readers after reviewing the radiographs again. All workers with silicosis were followed up until the end of 1999 to ascertain their vital status through various means. The diagnosis of tuberculosis was based on the results of sputum smear and/or culture.

We selected all underlying causes of death due to NMRDs other than pneumonia and infectious diseases (International

Abbreviations: CDE, cumulative dust exposure; COPD, chronic obstructive pulmonary disease; ICD, International Classification of Disease; ILO, International Labor Organization; MDC, mean dust concentration; NMRD, non-malignant respiratory disease; p-spline, penalised smoothing spline; SMR, standardised mortality ratio

Classification of Diseases (ICD), 9th revision: 490–519) for this study in order to focus on the conditions most plausibly associated with occupational exposure to silica dust. Tuberculosis was treated as a separate underlying cause of death. Considering a potential association between tuberculosis and exposure to silica dust, further data analyses were carried out to compare the dust effects with or without including tuberculosis in NMRDs. Deaths from COPD included chronic bronchitis (ICD code 491), emphysema (ICD code 492) and chronic airway obstruction not classified elsewhere (ICD code 496). No death was reported from extrinsic allergic alveolitis and asbestosis.

Retrospective exposure assessment

A master list of industries and job tasks was constructed using information from each worker's complete occupational history. Participants of this cohort could be categorised into surface construction workers (51%), underground caisson workers (37%) and workers in other dusty occupations (12%).[14] The most common job tasks related to exposure to silica dust were unskilled labouring, stone cutting, stone crushing machine attendance and pneumatic drilling. Surface construction workers were exposed to relatively low levels of free silica dust. Underground caisson workers were exposed to very high levels of silica dust and radon daughters, but were less likely to be exposed to diesel exhaust or oil mists, as the machine compressors (if used) were placed on the surface during caisson digging.[16] The Hong Kong method of caisson construction is usually described as a circular hole of 1–3 m diameter dug by hand to a depth of up to 1 m at which the surrounding soil will stand unsupported. The site is then lined with concrete and the excavation of the next stage starts and so on. Construction is more or less similar to the British ''middle-board'' and American ''Chicago'' methods, except that concrete rather than boarding is used as the outer support wall at each stage. Depending on circumstances, the caisson depth may range up to 50 m.[16] Manual excavation of soil and rock using hand shovel, pneumatic drill and hand wedge was the standard in local caisson practice. Workers in the group of other dusty occupations were those who had, in addition to silica dust, other occupational dust exposures and mainly included those ever employed in tunnelling, mining, and metal and iron manufacturing, and were potentially exposed to high levels of silica dust. In the subgroup analysis on exposure–response relationship, we combined the underground caisson workers with workers in other dusty occupations as the high exposure group.

A geometric mean concentration of respirable crystalline silica was assigned to each industry or job task by a panel of experts (including a senior occupational hygienist with experience in assessing exposure to silica), according to published occupational hygiene data on exposure to crystalline silica in Hong Kong[16–18] and their professional experience, who were blinded to the vital status of each worker. All available concentrations of respirable silica dust were assigned to each industry and job task to assess the occupational exposures to silica dust. CDE and MDC for crystalline silica were used as indices of exposure to silica dust. CDE (mg/m^3-year) was calculated by summing the products of the concentration of respirable silica dust and the duration of exposure to silica dust for all jobs in a worker's career lifetime. MDC (mg/m^3) was calculated by dividing the CDE by the total duration of exposure to silica dust. The changes in exposure intensity with the calendar year were not considered in the exposure assessment because of limited hygiene data available. Most of the workers were removed from exposure after the diagnosis of silicosis.

Statistical analyses

The standardised mortality ratio (SMR) of NMRDs and other specific causes was calculated as the ratio of the observed to the expected number of deaths. The 95% confidence interval (CI) for the SMR was derived assuming a Poisson distribution for the observed numbers.[19] The expected number of deaths was calculated by multiplying the age–period-specific person-years at risk by the corresponding death rates of the Hong Kong general male population. Smoking could be a confounder causing distortion of the association between silicosis and mortality from NMRDs and COPD, as the prevalence of ever smokers among those with silicosis (89.57%) was much higher than that among males of a similar age (51.30%) in the general population.[20] Smoking was adjusted by an indirect method proposed by Axelson and Steenland,[21] assuming a relative risk for mortality from NMRDs (or COPD) of 3.68 for the Hong Kong male population.[22]

Penalised smoothing spline (p-spline) models were used as a preliminary step to detect outliers and provide guidance for choosing the best simple Cox's proportional hazard model.[23 24] p-Spline curves for mortality from NMRDs (or COPD) showed an inversion of exposure–response relationship with both CDE and MDC at very high exposures. This inverse relationship probably resulted from the healthy worker survivor effect.[9 25] Based on this, we excluded from further NMRD mortality analysis subjects with CDE >40 mg/m^3-year or MDC >1.3 mg/m^3, and restricted COPD mortality analysis to CDE $\leqslant 60$ mg/m^3-year and MDC $\leqslant 1.75$ mg/m^3. The proportions of excluded workers with silicosis and the those with NMRDs or COPD were only 1.2–3%.

After right truncation of exposure, multiple Cox's proportional hazard models were used for both NMRD and COPD to fit a possible exposure–response relationship with CDE or MDC. Age at entry into cohort, history of tuberculosis, smoking status and calendar year of first exposure to silica—an indirect indicator of changes in dust exposure over time, if any—were regarded as potential confounding factors in the multiple analyses. As the correlations between exposure to silica dust and the confounders in the models were weak (all <0.5), inclusion of age at entry into cohort and history of tuberculosis in the models should not have overcontrolled for confounding effects. The goodness of fit for all models was evaluated by comparing the reductions in deviance. Models with the largest decrease in deviance with the addition of the exposure terms were considered to be best fitting.

RESULTS

The vital status was successfully ascertained in 2707 (97%) patients among the entire cohort of 2789 patients with silicosis during the follow-up period 1981–99. Death certificates or notifications were obtained for 809 (94.84%) from a total of 853 deaths. The average age at entry into cohort was 54.39 years and the mean duration of follow-up was 9 years, with 24 993 person-years of observation. The percentage of smoking was 89.57% (49.77% current smokers and 39.80% ex-smokers) and the mean pack-years was 28.24 among smokers. In all, 1355 (48.58%) patients had a history of tuberculosis.

Table 1 shows the main characteristics of the whole cohort stratified by occupational group. Workers in underground caisson and other occupations were significantly younger at the time of entry into cohort, but had smoked less heavily compared with surface construction workers. Despite the duration of exposure to silica dust being shorter for workers in caisson and other occupations, these workers had higher levels of cumulative exposures to silica dust because of the high intense exposure to silica dust. The pattern of severity of radiological silicosis at the time of diagnosis was quite similar

Table 1 Main characteristics and the exposure indices of exposure to silica dust by occupational group among a cohort of 2789 workers with silicosis in Hong Kong

	Surface construction	Underground caisson and other occupations
Subjects	1425	1364
Person-years	13 410	11 583
Smoking status,* n (%)		
Never smoker	152 (10.73)	124 (9.14)
Ex-smoker	582 (41.07)	528 (38.90)
Current smoker	683 (48.20)	705 (52.95)
Pack-years among smokers†	31.18 (0.5–202.5)	25.23 (0.1–160)
ILO categories of silicosis with small opacities only, n (%)		
1/0–1/2	438 (38.25)	485 (44.41)
2/1–2/3	574 (50.13)	499 (45.70)
3/2+	133 (11.62)	108 (9.89)
Patients with silicosis with large opacities	280 (19.65)	272 (19.94)
History of tuberculosis‡	715 (50.42)	640 (47.09)
Calendar year at the first exposure to silica dust (years)†	1956 (1917–90)	1962 (1924–84)
Age at diagnosis of silicosis (years)†	57.65 (28.37–89.72)	51.00 (27.74–87.3)
Duration of exposure to silica dust (years)†	25.99 (1–55)	23.28 (2–58)
Cumulative exposure to silica dust (mg/m^3-year)†	7.33 (0.05–25.85)	14.62 (0.09–139.63)
Mean dust concentration (mg/m^3)†	0.27 (0.003–0.5)	0.64 (0.005–4.23)

*Excluding 15 unknown smoking status.
†Mean (range).
‡Excluding 12 workers with unknown history of tuberculosis.
ILO, International Labor Organization.

between workers in caisson and other occupations and surface construction workers. The distribution of the smoking status, history of tuberculosis and calendar year at the first exposure were not significantly different between occupational groups.

We observed 371 (43%) deaths from NMRDs during the follow-up period 1981–99, giving an SMR of 8.48 (95% CI 7.64 to 9.39) and a smoking-adjusted SMR of 5.89 (95% CI 5.31 to 6.52). Silicosis constituted the major cause of death (243 deaths, 65.5%) among those with NMRDs, with an SMR of 458.49 (95% CI 402.65 to 519.91). COPD (101 deaths) accounted for 27.22% of NMRDs and had an SMR of 2.93 (95% CI 2.39 to 3.57) and a smoking-adjusted SMR of 2.03 (95% CI 1.66 to 2.48). Other examples of causes of death from NMRDs were bronchiectasis (3 patients, 0.81%), asthma (1 patient, 0.27%) or other unspecified NMRDs (23 patients, 6.20%). In addition, a total of 37 deaths were observed from tuberculosis, with an SMR of 5.94 (95% CI 4.39 to 8.59).

Exposure–response analyses for mortality from NMRDs

After right truncation of patients with CDE >40 mg/m^3-year (2% of all deaths from silicosis and 1.6% of those from NMRDs) or MDC >1.3 mg/m^3 (2.7% of all deaths from silicosis and 2.4% of those from NMRD deaths), results from multiple Cox's regression models for both CDE (hazard ratio (HR) 1.02, 95% CI 1.01 to 1.04, p = 0.009) and MDC (HR 2.47, 95% CI 1.58 to 3.84, p<0.001) showed a significant relationship with NMRD mortality (table 2). No significant differences were seen in the model fits between these two models. The risk of mortality from NMRDs among former smokers with silicosis was significantly increased and twice as high as that among never smokers, whereas such risk was not significantly increased among current smokers. Age at entry and history of tuberculosis were also significantly associated with death from NMRDs. Results from Cox's regression analyses were not changed after including deaths from tuberculosis in NMRDs.

Exposure–response analyses for mortality from COPD

As that for NMRDs, the right truncated Cox's models for CDE ($\leqslant$60 mg/m^3-years, excluding 1.2% of patients with silicosis and 1% of COPD deaths) or MDC ($\leqslant$1.75 mg/m^3, excluding 2% of patients with silicosis and 3% of COPD) showed that people with silicosis who were ex-smokers had about three times the risk of mortality from COPD compared with the lifelong never smokers. Current smokers also had increased risk of COPD mortality, but the association was not statistically significant. A borderline association was seen between death from COPD and MDC (HR 1.92, 95% CI 0.91 to 4.06, p = 0.089). Cox's regression model for risk of COPD mortality fitted with MDC was only slightly better than that with CDE. Nevertheless, duration of exposure to silica dust was inversely related to the risk of death from both NMRDs and COPD. The goodness of fit of the MDC model was not superior to that of the CDE model for either NMRDs or COPD mortality.

Subgroup analyses by occupational group

Workers ever employed in caisson and other occupations had 50% higher risk of dying from NMRDs than surface construction workers, whereas the increased risk of COPD was not significantly different between occupational groups (table 3). After right truncation as mentioned above, deaths from NMRDs and COPD for workers ever employed in caisson and other occupations were significantly associated with exposure to silica dust for both CDE (p = 0.002 for NMRDs and p = 0.044 for COPD) and MDC (p = 0.004 for NMRDs and p = 0.040 for COPD). No association was detected between mortality from NMRDs or COPD and CDE or MDC among surface construction workers with lower levels of exposure.

Analyses of radiographic opacities

Multiple Cox's proportional hazard regression analyses among all workers with silicosis showed that workers with large opacities had significantly increased risk of dying from NMRDs and COPD by 109% (95% CI 66% to 163%, p<0.001) and 59% (95% CI 1% to 151%, p<0.045), respectively. A clear upward trend for both NMRD and COPD was found with the increasing stage of large opacities, whereas such a trend was less marked with the profusion of small opacities, especially for COPD (table 4). These trends remained unchanged after adjusting for the dust effects (both CDE and MDC).

Results from the exposure–response analyses between various indices of exposure to silica dust and the deaths from NMRDs or COPD were virtually unchanged when smoking

Table 2 Exposure–response relationships between mortality from non-malignant respiratory diseases or chronic obstructive pulmonary disease and the cumulative exposure to silica dust or mean dust concentration using multiple Cox's regression model after truncations

Predictor variable	HR and 95% CI of NMRD*	HR and 95% CI of COPD†
Modelling cumulative exposure to silica dust		
Cumulative exposure to silica dust (mg/m^3-year)	1.02 (1.01 to 1.04)	1.01 (0.98 to 1.03)
Age at entry (years)	1.05 (1.03 to 1.06)	1.04 (1.01 to 1.07)
Smoking status		
Never smoker	1	1
Ex-smoker	2.24 (1.44 to 3.5)	3.15 (1.13 to 8.76)
Current smoker	1.47 (0.94 to 2.29)	2.48 (0.90 to 6.88)
History of tuberculosis	1.30 (1.05 to 1.61)	1.44 (0.96 to 2.15)
Calendar year at first exposure	1.03 (1.02 to 1.04)	0.99 (0.97 to 1.02)
Change in deviance with the addition of CDE	6.52	0.38
Modelling mean dust concentration		
Mean dust concentration (mg/m^3)	2.47 (1.58 to 3.84)	1.92 (0.91 to 4.06)
Years of exposure to silica dust	0.98 (0.97 to 1)	0.95 (0.93 to 0.97)
Age at entry (years)	1.05 (1.03 to 1.06)	1.04 (1.01 to 1.07)
Smoking status		
Never smoker	1	1
Ex-smoker	2.17 (1.39 to 3.39)	2.82 (1.01 to 7.87)
Current smoker	1.43 (0.92 to 2.24)	2.31 (0.83 to 6.39)
History of tuberculosis	1.29 (1.05 to 1.60)	1.42 (0.94 to 2.13)
Calendar year at first exposure	1.01 (1 to 1.03)	0.95 (0.93 to 0.98)
Change in deviance with the addition of MDC	4.18	2.70

*Restricting CDE to $\leqslant 40$ mg/m^3-year or MDC to $\leqslant 1.3$ mg/m^3 for NMRD.
†Restricting CDE to $\leqslant 60$ mg/m^3-year or MDC to $\leqslant 1.75$ mg/m^3 for COPD.
CDE, cumulative dust exposure; COPD, chronic obstructive pulmonary disease; MDC, mean dust concentration; NMRD, non-malignant respiratory diseases.

pack-years was replaced by smoking status in the multiple Cox's proportional hazard models.

DISCUSSION

This retrospective cohort study showed excess risk of death from NMRDs and COPD among 2789 workers with silicosis in Hong Kong, with smoking-adjusted SMRs of 5.89 and 2.03, respectively. The risk of dying from NMRDs and COPD was particularly high in the subgroup that had worked in underground caisson and other occupations where a very high level of silica dust existed. By right truncating the observations with high levels of exposure to silica dust, a clear exposure–response relationship was seen between exposure to silica dust and the mortality from NMRDs. For COPDs, the relationships were in the same direction but slightly weaker and did not achieve statistical significance, owing to inadequate power resulting from the smaller number of COPD deaths. However, after excluding surface construction workers, who are usually exposed to lower levels of silica dust, the exposure–response became stronger and statistically significant.

The principal merit of this study is that this is the first study to specifically compare the exposure–response relationship of CDE or MDC with the risk of dying from NMRDs or COPD after considering the effect of cigarette smoking. Inadequacy in historical exposure data posed a limitation. Nevertheless, exposure assessments were performed with the assessors

Table 3 Hazard ratios and 95% CI of subgroup analyses by occupational group for the association between mortality from non-malignant respiratory diseases or chronic obstructive pulmonary diseases and exposure to silica dust

Predictor variable	HR and 95% CI of NMRD	HR and 95% CI of COPD
Occupational groups (no restriction on CDE or MDC)*		
Surface construction	1	1
Underground caisson and other occupations	1.50 (1.21 to 1.87)	1.19 (0.79 to 1.81)
Subgroup analyses on cumulative exposure to silica dust (CDE $\leqslant 40$ mg/m^3-year for the analysis with NMRD and CDE $\leqslant 60$ mg/m^3-year for COPD)†		
Surface construction	0.98 (0.95 to 1.00)	0.95 (0.90 to 0.99)
Underground caisson and other occupations	1.03 (1.01 to 1.05)	1.03 (1.00 to 1.05)
Subgroup analyses on MDC ($\leqslant 1.3$ mg/m^3 for the analysis with NMRD and MDC $\leqslant 1.75$ mg/m^3 for COPD)‡		
Surface construction	0.88 (0.39 to 2.03)	1.56 (0.13 to 2.38)
Underground caisson and other occupations	2.53 (1.38 to 4.66)	2.72 (1.05 to 7.05)

*Variables in the multiple Cox's regression model include occupational groups, age at entry, history of tuberculosis, smoking pack-years and calendar year of first exposure, using surface construction as reference.
†Variables in the multiple Cox's regression model included CDE, age at entry, history of tuberculosis, smoking pack-years and calendar year of first exposure.
‡Variables in the multiple Cox's regression model included MDC, age at entry, history of tuberculosis, smoking pack-years, duration of exposure to silica dust and calendar year of first exposure.
CDE, cumulative dust exposure; COPD, chronic obstructive pulmonary disease; MDC, mean dust concentration; NMRD, non-malignant respiratory diseases.

Table 4 Exposure–response relationship between radiological severity of silicosis and mortality from non-malignant respiratory diseases or chronic obstructive pulmonary diseases among all workers with silicosis, using multiple Cox's regression

Exposure indices	NMRD	COPD
Small opacities*		
1	1.0	1.0
2	1.14 (0.84 to 1.55)	0.92 (0.54 to 1.58)
3	1.79 (1.23 to 2.63)	1.23 (0.60 to 2.53)
Large opacities†		
A	1.0	1.0
B	1.95 (1.30 to 2.94)	1.56 (0.65 to 3.75)
C	4.53 (2.64 to 7.78)	5.71 (2.02 to 16.20)

*Model restricted to subjects with small opacities only and adjusted for age at entry, smoking pack-years, history of tuberculosis and calendar year of first exposure.
†Model restricted to subjects with large opacities only and also adjusted for age at entry, smoking pack-years, history of tuberculosis and calendar year of first exposure.
COPD, chronic obstructive pulmonary disease; NMRD, non-malignant respiratory diseases.

blinded to the vital status of each patient, thus largely reducing the possibility of systematic misclassification.

The exposure–response relationship with NMRD mortality reported here was restricted to a CDE of crystalline silica <40 mg/m^3-year. A similar trend was observed among diatomaceous earth workers in California after excluding CDE >10 mg/m^3-year (representing 3% of follow-up and 16% of deaths from NMRDs),[9] but the peak of the exposure–response curve shifted towards lower exposure compared with our study; the different toxicities of quartz polymorphs (eg, diatomaceous earth workers in California were mainly exposed to cristobalite, but workers with silicosis in Hong Kong were mainly exposed to crystalline silica) might explain the variations. Nevertheless, the inversion in exposure–response relationship with increasing CDE in the highest exposure region observed in both the California and our cohorts might be a reflection of an exhaustion of susceptible workers at high exposures (healthy-worker effect), saturation of biological pathways or mismeasurement at high exposures.[9 25] We believe that restricting the analysis to workers exposed to a low to medium level may help to reduce some forms of biases. Two other studies, Kansas fiberglass manufacture[7] and UK quarries,[26] did not show a clear exposure–response relationship between NMRDs and CDE. The relatively low level of exposure to silica dust of these two studies may be the reason for the negative findings, as in the low-dose region it is hard to determine the shape of the exposure–response curve.[27] In our study, the exposure–response relationship between NMRD mortality and CDE was found only in underground caisson and other occupations where a relatively high level of silica dust existed. No positive exposure–response relationship could be detected among our surface construction workers exposed to a relatively low dose of silica dust (MDC generally <0.5 mg/m^3). The patterns of the exposure–response relationship with exposure to silica dust observed from our study are in line with other findings.[7 9 26]

Many previous studies have dealt with the exposure–response trends for NMRDs or silicosis using various indices of silica dust,[4 9 12 13 28–30] but few have specifically discussed the limitations in the use of CDE.[13] Principally, exposure–response models of CDEs should be based on the assumption that the internal biologically significant dose is a linear function of both concentration and duration of exposure.[11 13] These assumptions, however, may be violated at higher intensity exposures (eg, >0.5 mg/m^3).[11] In this case, non-differential misclassification would be introduced and a possibly attenuated effect of CDE would be anticipated.[11 13 31] Epidemiological evidence showed that a substantially steeper relationship with silicosis was observed among workers exposed to short but high concentration than a long but low exposure at a similar cumulative level >2 mg/m^3-year.[12 13] This suggests that dust concentration would be of great importance in predicting the risk, especially at high intense exposure.[11] Theoretically, the human respiratory system has the ability to clear inhaled dust as well as self-healing. A low-dose long-duration exposure can be less harmful than a higher dose exposure of shorter duration (with equivalent CDE), as natural defences will be able to clear and compensate in time before the threshold is exceeded. However, short intense exposure might produce a very large integrated tissue dose, thus lengthening the time of residence of retained dust in the lung, and slow down alveolar clearance, ultimately providing an increased opportunity for pathological processes in the lungs.[11] Results from our study showed similar model fits for MDC and CDE, suggesting that both MDC and CDE were important indices of exposure to silica dust in examining the exposure–response relationship with NMRDs.

It is assumed that exposure to silica or mineral dust containing a large percentage of silica would result in emphysema and pathological changes in lung parenchyma other than silicosis.[32] However, epidemiological evidence on the exposure–response relationship between exposure to silica dust and COPD is inconclusive. Hnizdo *et al* found an exposure–response relationship between CDE and COPD (or emphysema) according to autopsy data among South African gold miners.[2 32] Calvert *et al*[4] also found a positive relationship with exposure to crystalline silica based on death certificates from 27 US states. However, Cocco *et al*[33] did not observe an association of chronic bronchitis with any indicator of dust exposure among Chinese workers exposed to silica. In our study, mortality from COPD was significantly associated with both CDE and MDC among workers ever employed in underground caisson and other occupations where high doses of silica dust were often detected. No association was found among our surface construction workers with low dust exposure. As in the case of NMRDs, the exposure–response relationship with COPD is difficult to determine in the low-dose region.

A strong positive trend for death from NMRDs was found with the profusion of small opacities or large opacities among our workers with silicosis. Our findings are consistent with those of US diatomaceous earth workers,[9] and those with silicosis in Michigan and New Jersey.[5] Thus, the presence of large opacities and the increasing profusion of small opacities seem to be reliable markers of increased risk of death from NMRDs. The role of severity of silicosis in death from COPD was less clear, but this may have been due to insufficient numbers of deaths from COPD in the various radiographic categories in our cohort. The presence of large opacities on chest radiograph might be misclassified as the mass of tuberculosis. However, as the diagnosis and classification of silicosis was dependent on a panel of experts rather than on an individual doctor, such misclassifications should be minimal.

We found that workers with silicosis who had stopped smoking at the time of entry into the cohort (diagnosis of silicosis) were at the highest risk of dying from NMRDs, especially COPDs compared with current and never smokers with silicosis. Ex-smokers probably had to stop smoking because of the development of serious respiratory symptoms or emphysema; current smokers might represent ''healthy smokers'' (ie, survivor selection bias) who experienced lower risk of death from both NMRDs and COPD than the ex-smokers.

Main messages

- An exposure–response relationship between exposure to silica dust and risk of death from non-malignant respiratory diseases (NMRDs) or chronic obstructive pulmonary diseases was documented among workers with silicosis in Hong Kong.
- Independently of dust effects, the risk of mortality from NMRDs increased considerably with the progression of radiological International Labor Organization categories.

Policy implications

- To reduce deaths from non-malignant respiratory diseases or chronic obstructive pulmonary diseases among workers exposed to silica dust, it is recommended that less hazardous materials be substituted for crystalline silica where feasible, or engineering controls be used to reduce dust concentrations in the workplace air to a safe level.

Possibly, some deaths from COPD had been misdiagnosed as caused by silicosis. Such misclassification, if present in our study, was believed to be within a similar range to other studies on silicosis, because of a comparable proportion of deaths from silicosis obtained in these studies.[34 35] Misclassification of the underlying cause of death was possible but most likely to be non-differential, and would thus cause the association to tend towards null.[14] Censoring deaths from silicosis in the COPD mortality analysis might be problematic, as the age at death from silicosis (62.08 years) was about 2 years earlier than that from COPD (64.58 years). Deaths from silicosis might have competed with deaths from COPD. As a consequence, the association between exposure to silica dust and COPD might have been underestimated.

CONCLUSION

This retrospective cohort study showed a substantially increased mortality from NMRDs and COPD among people with silicosis in Hong Kong. An exposure–response relationship between exposure to silica dust and the risk of death from NMRDs or COPD was documented among workers with silicosis, except for the surface construction workers with low exposures. The risk of mortality from NMRDs increased significantly with the progression of radiographic ILO categories, independent of dust effects. Both MDC and CDE were effective indices of exposure to silica dust in detecting the exposure–response relationships with mortality from NMRDs and COPD.

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